Phase 1/2 study of Ad/PNP with fludarabine for the treatment of head & neck squamous cell carcinoma

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Background

We are evaluating intratumoral nucleoside cleavage by E. coli purine nucleoside phosphorylase (PNP) as an experimental therapy for refractory solid tumors. The approach requires delivery of PNP transgene to tumor parenchyma followed by prodrug administration and provides "bystander" killing by a very potent purine antimetabolite (F-Ade) generated intratumorally. F-Ade is 1,000 times more active than fluorouracil, the chemotherapeutic produced by cytosine deaminase (CD), a first-generation construct used for tumor sensitization. PNP-Ade has been found superior to CD/fluorouracil by several laboratories. In a Phase 1 study (Rosenthal et al., Ann Oncol), antitumor activity was observed following IT injections of a recombinant adenovirus encoding PNP (Ad/PNP), followed by IV fludarabine phosphate (F-araAMP), a prodrug converted by PNP to F-Ade.

Robust and dose dependent tumor regressions in animal models using a PNP based approach

Study Progress

Patients in the present Phase 1/2 trial have RESS1 1.1 measurable tumors amenable to local injection and no other palliative treatment options. A single-arm protocol is being used to evaluate safety of repeat cycles of Ad/PNP and F-araAMP. Ad/PNP (Gendex5®) is injected intratumorally twice on Day 1 and once on Day 2, followed by infusion of F-araAMP on Days 3, 4, and every 4 weeks for up to 5 cycles.

**Method**

**Progress to date**

**Table 1. Schematic of Phase I Clinical Trial**

<table>
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<tr>
<th>Patient</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Age (yr)</th>
<th>Tumor type</th>
<th>Number of cycles</th>
<th>Target lesions</th>
<th>Response</th>
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<td>PB</td>
<td>PR</td>
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<td>HNSCC</td>
<td>3</td>
<td>N/A</td>
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</tr>
</tbody>
</table>

**Figure 1. Predrug activation by E. coli PNP.** Fludarabine is cleaved to liberate F-Ade, a compound that disrupts DNA, RNA, and protein synthesis.

**Figure 2. Adverse events by SOC (System Organ Class).**

**Table 2. Demographic and treatment related data in individual patients.**

**Table 3. Schematic of Ad/PNP and Fludarabine treatment for individual patients**

**Figure 3. Tumor response by dose and iteration.**

**Figure 4. Adverse events attributable to study drug.**

**Figure 5. Adverse events by relationship to the drug.**

**Figure 6. Adverse events attributable to treatment.**

**Figure 7. Adverse events attributable to study drug.**

**Figure 8. Adverse events by relationship to the drug.**

**Figure 9. Adverse events by grade.**

**Table 4. Schematic of Ad/PNP and Fludarabine treatment for individual patients**

**Table 5. Schematic of Ad/PNP and Fludarabine treatment for individual patients**

**Ad/PNP Insights**

- Evidence of antitumor activity. Stable disease noted in 5 of 8 patients in treated tumors.
- In the current Phase 1/2 trial, there have not been any dose limiting toxicities or serious adverse events (SAEs) definitively attributable to treatment.
- One patient with HNSCC has demonstrated tolerability of 5 treatment cycles without limiting sequelae.
- The strategy is also being considered for earlier-stage HNSCC with less tumor burden, including a role similar to neoadjuvant or cytoreductive radiotherapy in combination with checkpoint blockade inhibition.
- A multi-center trial is planned to define MTD and feasibility in smaller tumors.
- Challenges:
  - Reductions of large tumors remains a challenge, likely due to the low percentages of PNP transduced cells achieved with small volume Ad/PNP injections.
  - Acute swelling of tumor tissue following intratumoral virus injection has been observed in two patients, consistent with inflammatory response and/or disease progression.

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